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Application of the threshold of toxicological concern approach to ingredients in personal and household care products

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Abstract

In the absence of chemical-specific data, the threshold of toxicological concern (TTC) provides a method to determine a conservative estimate of a chronic oral exposure below which there is a very low probability of risk. The TTC approach was originally developed to support exposures to indirect food additives and was based on linear low-dose risk estimates to assure protection in the event that the chemical was later determined to be a carcinogen. Subsequently, TTC values based on noncancer endpoints were proposed for chemicals without structural alerts for genotoxicity. The original database supporting the TTC values for noncancer endpoints includes >600 structurally diverse chemicals. The objectives of this work were to evaluate the applicability of the TTC database to ingredients used in consumer products based on a comparison of the diversity of chemical structures with those in the original TTC database and to confirm that the range of NOELs for these ingredients is consistent with the range of NOELs in the original database. The results show good coverage of the product ingredient structures and confirm that the NOELs for the ingredient chemicals are similar in range to the original dataset, supporting the use of the TTC for ingredients in consumer products.

Keywords: Threshold of toxicological concern; *De minimus* risk; Structure–activity; Toxicological risk assessment

1. Introduction

The threshold of toxicological concern (TTC) approach is used to estimate a conservative threshold of human exposure below which "there would be no appreciable risk to human health" (Kroes et al., 2004). TTC approaches designed to be protective for both cancer and noncancer endpoints have been proposed. An integrated decision tree that describes the application of the TTC values for both cancer and noncancer endpoints was developed as the outcome of a European International Life Sciences Institute (ILSI-Europe) workgroup and is described in Kroes et al. (2004). The current discussion focuses on the use of TTC values for noncancer endpoints as described in Munro et al. (1996) and further elaborated in Kroes et al. (2004). The TTC approach has primarily been used to evaluate indirect food additives, and more recently low level, direct food additives (WHO, 2002). Given current concern for animal use and the proposed future ban on animal testing of cosmetic ingredients in the Europen Union, nonanimal methods to assess ingredient/contaminant safety are urgently needed. Analyses of the time required to develop validated in vitro or in silico alternatives for repeat-dose toxicity endpoints, even with significant investment of resources, indicate that these methods are unlikely to be available in the foreseeable future (European Commission, 2004). Given that consumer protection is of paramount importance, methods that can be used to assure consumer safety to low level exposures to ingredients or contaminants and that

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help to minimize and prioritize testing resources while providing a foundation for maintaining high standards for consumer safety are clearly desirable.

In the integrated framework described by Kroes et al. (2004), chemicals that are possibly genotoxic/carcinogenic as determined by the presence of structural alerts are segregated from chemicals that lack alerts. Chemicals with alerts are screened for structures that are potentially associated with very high carcinogenic potency (aflatoxin-like, azoxy, and *N*-nitroso); these are excluded from the TTC approach, although another option would be to establish a more conservative TTC exposure limit for these high potency carcinogens. The remaining chemicals with structural alerts for genotoxicity are assigned a TTC value of 0.15 μg/day based on the distribution of risk levels for the database of carcinogens (i.e., the Carcinogen Potency Database compiled by Gold et al., 1984, 1989), determined using low dose linear extrapolation.

The TTC approach for chemicals that lack structural alerts or other evidence for genotoxicity/carcinogenicity is based on the principle that noncancer toxicological effects exhibit a threshold dose, and that a conservative estimate of a sub-threshold dose for an untested chemical can be based on the distribution of NOELs for a large group of tested chemicals. The approach is based on grouping chemicals into three broad potency classes based on structural features that correlate with toxicity. It is important to distinguish this approach from a QSAR approach in that there is no attempt to predict the NOEL for an unknown chemical based on structure. Rather, this approach is based on the assumption that the NOEL for a chemical will not be significantly lower than the lower boundary (i.e., the 5th percentile) of the population of NOELs for the other chemicals that fall into the same broad structure-based potency grouping. This approach is designed to be conservative, such that it is much more likely that the NOEL value for the untested chemical will be higher than the TTC value, rather than lower than the TTC value.

Munro et al. (1996) described the TTC framework in which chronic oral NOELs were located from literature sources (or calculated from subchronic oral studies) for 613 compounds, including pesticides, food additives, and industrial chemicals. The compounds were grouped into three potency classes based on chemical structure using a decision tree approach described by Cramer et al. (1978) and later refined by Phillips et al. (1986), referred to here as "Cramer Classes." The decision tree consists of a series of 33 questions regarding chemical structure that are used to classify a chemical as either Class I (a low order of oral toxicity), Class II (indeterminate toxicity, no presumption of safety or significant harm); or Class III (no strong presumptions of safety; structure may even suggest significant toxicity). The assignment of each of the 613 compounds to its appropriate Cramer Class resulted in a distribution weighted towards Class III: there were 137 chemicals in Class I, 28 chemicals in Class II, and 448 chemicals in Class III. Munro et al. (1996) then calculated the fifth percentile value from the distribution of NOELs for each class. Human exposure thresholds (in mg/day) for the three Cramer classes were based on the fifth percentile NOEL, an assumed human body weight of 60 kg, and a safety factor[1] of 100 (Munro et al., 1996). The 100-fold safety factor was considered to provide an adequate margin-of-safety considering the size of the database and the nature of the supporting toxicological data. These human exposure thresholds were recommended as TTC exposure limits for the three Cramer Classes (1.8 mg/day for Class I; 0.54 mg/day for Class II, and 0.09 mg/day for Class III). Endpoints that were identified to be of special concern were evaluated in separate subset analyses (e.g., neurotoxicity[2], reproductive/developmental toxicity) and were shown to have a distribution of NOELs that was similar to the distribution of NOELs observed for target organ toxicity (as measured in a subchronic or chronic study). Therefore, it was not considered necessary to develop endpoint-specific human exposure threshold values (Kroes et al., 2004).

A primary question in extending the TTC approach to the chemicals used in personal and household care products is whether or not the chemical structures used in the original analysis (Munro et al., 1996) reflect the range of chemical structures used in these consumer products. To address this question, a list of chemicals known to be currently or historically used as ingredients in either household (fabric or hard surface) or personal care products was compiled and used as a guide for selecting compounds for the present analysis. As a first step, these chemicals were stratified by both chemical structural category and TTC potency classes as described below. This stratified list of chemicals was used to identify chemicals for retrieval of toxicity data and identification of a set of NOEL values that could be compared to the NOELs from the original TTC analysis presented in Munro et al. (1996).

2. Methods

2.1. Personal and household care product ingredients compared to chemicals in the threshold of toxicological concern dataset

To evaluate the relevance of the TTC values calculated in Munro et al. (1996) to chemicals used in personal and household care products, it is important to have confidence that the chemicals used in the original analysis represent a diversity of chemical structures sufficient to cover the chemical structures represented by chemicals used in these products. In addition, if there are chemical structures used

[1] "Safety factor" is the terminology used by Munro et al. (1996); some regulatory agencies have opted for the use of the term "uncertainty factor."

[2] With the exception of organophosphates, which were shown to be associated with a higher degree of toxicity that warrants its own TTC exposure limit.

in personal and household care products that were not represented in the original analysis, it is important to confirm that these chemicals have NOEL values that are within the range of NOEL values of the chemicals in the original analysis.

To compare the structures of the chemicals used in the Munro et al. (1996) paper to a list of personal and household care product ingredients, a framework for categorizing chemicals based on chemical structure was developed. The chemical categories used by the Cosmetic Toiletries and Fragrance Association (CTFA; www.ctfa-online.org) were used as a starting point. This system defines 66 categories, predominately based on chemical structure (e.g., alcohols, ketones, and sterols). The number of categories was expanded to 92 for this exercise since there were chemicals analyzed in the original TTC analysis (Munro et al., 1996) that did not fit into any of the CTFA categories. These categories are listed in Appendix A. These predominately structural categories (there are a few categories based on nonstructural criteria such as color additives) should not be confused with the Cramer Classes. The chemical categories are not based on any a priori assumption of toxic potency, but are used solely as a tool to characterize the range of chemistries included in the Munro et al. (1996) analysis as compared to ingredients used in personal and household care products.

The following describes the approach used for data selection in our analysis:

- A list of ingredients was retrieved from an internal Procter and Gamble electronic archive of ingredients with a history of use in personal care or household care products.
- To streamline the search for relevant subchronic data, this list was cross searched against a second Procter and Gamble database indicating the availability of repeat dose toxicity studies from both internal and external sources. This resulted in a list of 248 ingredients with a history of use in personal care or household care products and with a notation for a repeat dose study.
- Of the 248 chemicals, 29 were found to be in the original Munro database. Excluding these resulted in a list of 219 chemicals unique to personal and household care products.
- These 219 chemicals along with the 613 chemicals from the Munro et al. (1996) database were grouped into the 92 chemical categories described above. These categories were not exclusive, i.e., a chemical could be placed in more than one category. Categories containing product ingredient chemicals, but without representation in the Munro et al. (1996) analysis were identified.
- In parallel, the 219 ingredients were reviewed and classified if possible via the Cramer et al. (1978) decision tree. One hundred forty five ingredients were classified via the Cramer et al. (1978) decision tree. The remaining compounds could not be classified because they did not fit the decision tree analysis for various reasons. These included substances such as large polymers, inorganic salts (e.g., potassium carbonate) or materials with undefined structures (e.g., mineral oil).
- The 145 ingredients were grouped into the three Cramer Classes. Within each Cramer Class, ingredients were listed in alphabetical order. The order of these lists was maintained during the review and selection process.
- The chemical category designations were noted for each of the 145 chemicals.
- Each of the three Cramer Class lists of personal and household care product ingredients was first evaluated for chemical categories not included in Munro et al. (1996). As these chemicals were exhausted, or as it was determined that adequate oral toxicology studies could not be located, additional chemicals were selected from the Cramer Class lists in alphabetical order.

The goal of this research was to select a subset of 20 chemicals per Cramer Class and to compare the range of NOELs for these chemicals with a history of use in personal and household care products with those used in the original Munro database. The goal of 20 chemicals per Cramer class represents a compromise between the ideal (evaluating data on all personal care chemicals with oral toxicity data) and the practical, based on resource constraints. It is emphasized that the goal of this work was not to recalculate the TTCs for each Cramer class, but rather to confirm that the range of NOELs for chemicals used in personal care products was no lower than the range of NOELs from the original Munro database that was used to establish the TTC exposure limits.

As one might expect, many of the personal and household care product chemicals had been tested in dermal or inhalation study protocols or in matrices that were relevant to product exposures. These studies, while appropriate given the intended use of the chemicals, were not considered appropriate for direct comparison to the Munro et al. (1996) list which included only oral toxicological studies of chemicals in simple vehicle (gavage or drinking water) or in diet. Specifically, we excluded studies that were done on whole products or complex formulations designed to simulate complex product matrices. This exercise resulted in oral toxicological data being found and deemed acceptable in the context of this project for a total of 45 personal and household care product ingredients: 22 chemicals in Class I; 2 chemicals in Class II; and 21 chemicals in Class III. For many of the chemicals the studies located were quite old. This is consistent with the low toxic potency of many of these chemicals and their long history of safe use and the resulting lack of impetus for additional studies. While many of these studies would not meet current regulatory test guidelines, they were all reviewed for scientific credibility, particularly if they had not already been reviewed in detail by a regulatory body or other expert group. The criteria used for evaluation are consistent with those outlined for the OECD screening information datasets (SIDs) evaluations based on the Klimisch scoring system. Studies meeting criteria consistent with

scores or 1 or 2 were considered acceptable for the present evaluation if they also met the further criterion of being consistent with other supporting data. These criteria as cited in OECD (2004) are:

1. *Reliable without restrictions*: "studies or data ... generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline... or in which all parameters described are closely related/comparable to a guideline method."
2. *Reliable with restrictions*: "studies or data... (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."

2.2. Review of toxicological data

Reliable secondary sources were consulted for toxicological data pertinent to the identification of chronic or subchronic oral NOELs. These included National Toxicology Program (NTP) reports, Cosmetic Ingredient Review (CIR) publications, the International Union Chemical Information Database (IUCLID), OECD Screening Information Datasets (SIDS), and Initial Assessment Report (SIAR) reports, Research Institute of Fragrance Materials (RIFM) Monographs, British Industrial Biological Research Association (BIBRA) reviews, and JECFA and other WHO reports (located via IPCS INCHEM at www.inchem.org). In the event that secondary sources were more than 5 years old, a search of scientific literature (Toxline and Medline) was conducted to identify pertinent toxicological studies conducted since the publication of the secondary source.

2.3. Selection of critical studies and identification of the animal NOEL

Oral studies using laboratory rodents or rabbits (excluding studies in dogs and other species) using simple vehicles or dietary exposure were reviewed. In the event that multiple studies were available for a particular compound, these studies were compared to ensure that the most sensitive toxicological endpoint and the lowest NOEL/LOEL were selected in accordance with the approach described by Munro et al. (1996). Subchronic, chronic, and reproductive and developmental toxicity studies were preferred for NOEL derivation, consistent with the original analysis[3]. However, several 28-day studies were also used in the absence of other available data. To meet European Union requirements under the Dangerous Substances Directive (ILO, 2001), personal and household care products ingredients are often tested in 28-day studies. They were included in this analysis to address as many of the personal and household care product chemicals in under-represented categories as possible. In this report, both "free-standing NOELs" (i.e., NOEL values from studies that did not show any effects at the highest dose tested, hence these values may be very conservative and may fall far below the threshold region of the dose–response curve) and "free-standing LOELs" (i.e., LOEL values from studies showing effects at the lowest dose tested) were used in the absence of other available data. Secondary review sources were used as a basis for the NOEL and LOEL values if they clearly called out these values, or if they provided sufficient details to determine the study NOEL or LOEL value. If insufficient information was provided, the primary source was obtained and reviewed.

2.4. Adjustment of NOELs

To create a database of chronic NOELs for comparison with the data from Munro et al. (1996), uncertainty factors (UFs) were applied to extrapolate from subchronic to chronic, from a subacute study (28- to 42-day studies) to subchronic study, and from a LOEL to a NOEL. Following Munro et al. (1996), a UF of 3 was used to extrapolate from a NOEL in a subchronic study to a chronic NOEL. An additional UF of 3 was used to extrapolate from a NOEL in a subacute study to a NOEL in a subchronic study (Kalberlah et al., 2003; ILO, 2001). This value is consistent with the use of 3 in the original publication, in that it represents the central tendency of the span of values for ratios of NOAELs from 28-day studies when compared to subchronic studies rather than the extremes of the range.

LOEL values were not used in the Munro et al. (1996) analysis, but were utilized here to include as many personal and household care product ingredients as possible from the stratified chemical groupings. None of these values were based on frank toxicity. We also employed a UF of 3 to extrapolate from a LOEL value to a NOEL. The default value most commonly used as a maximum for both the subchronic to chronic extrapolation and the extrapolation from LOAEL to NOAEL is 10, with 3 representing more of a central estimate (Dourson et al., 1996; Kalberlah et al., 2003). LOEL values from 28-day studies were not used due to the excessive uncertainty associated with extrapolating from these values to chronic NOELs. Thus, the greatest UF that could be applied to the data for a given compound was 10, reflecting the product of two UFs of 3 each (e.g., from a LOEL in a subchronic study to a chronic NOEL, or from a NOEL in a 28-day study to a chronic NOEL). Note that the resulting values represent the equivalent of chronic rodent NOELs; they have not

[3] The appropriateness of including reproductive and developmental toxicity endpoints in the TTC analysis was reaffirmed by Kroes et al. (2004).

been adjusted for interspecies and intraspecies uncertainties.

3. Results

There was considerable overlap between the chemical categories represented in the original Munro analysis and those represented by the personal and household care product ingredients. Of the 92 categories that were defined, 63 had representatives from the product ingredients, and of these 63 categories, only eight showed representatives from products with no representatives from the Munro et al. (1996) dataset indicating very good representation of the types of chemical structures used as product ingredients in the original analysis. The eight categories not represented in Munro et al. (1996) were:

- Alkoxylated amines: two alkoxylated amines were identified, one was a large polymer and therefore was not considered appropriate for classification via the Cramer decision tree and the other was ethanolamine (included in the present analysis);
- Alkoxylated carboxylic acids: two were identified; both were large polymers;
- Alkyl sulfates: one was identified and included in the present analysis (sodium lauryl sulfate);
- Benzophenones: two were identified and both are included in the present analysis (benzophenone and benzophenone-3);
- Betaines: one was identified (cocamidopropyl betaine), but an adequate oral study was not located;
- Fatty acids: five were identified (lauric, palmitic, oleic, stearic, and coconut fatty acids), but adequate oral studies were not located;
- Glyceryl esters: one was identified (glyceryl oleate), but no adequate oral study was located;
- Sarcosine derivatives: two were identified (sodium lauryl sarcosinate and isopropyl lauroyl sarcosinate); an adequate oral study was not located for the latter compound.

Oral NOELs were identified for a total of 45 product ingredients. The study types for these NOELs are summarized in Table 1 with details in Appendix B. The term "Adjusted NOEL" indicates the study NOEL/LOEL that has been adjusted using UFs specified previously. As the table indicates, most of the adjusted NOELs (30 of 45) are based on NOELs identified in chronic or subchronic studies. Only eight NOELs employ data from 28- to 42-day studies, and only five are based on LOELs.

Table 1
Basis for calculated NOELs

Basis for calculated NOEL	Number of compounds
Chronic NOEL	14
Chronic LOEL	2
Subchronic NOEL	16
Subchronic LOEL	2
28- to 42-Day NOEL	8
Reproductive/teratology	3
Total	45

The distribution of compounds by Cramer Class is shown in Table 2. Of the product ingredients considered for analysis in this paper, only a few fell into Cramer Class II. This is consistent with the data reported by Munro et al. (1996). In this report a larger percentage of compounds were categorized in Class I (63%; lowest toxicity) than in Class III (34%; highest toxicity). This finding is not surprising, given that compounds routinely used in personal care products would be expected to have a low order of toxicity. The range and geometric mean of NOELs from the Munro database and from the personal and household care ingredients is shown in Table 3 and summarized below. Our analysis shows that the NOEL values identified in this sample of product ingredients for each Cramer Class falls well within the range of NOEL values reported in Munro et al. (1996)[4]. The geometric mean is very similar for Cramer Class I chemicals whereas for Cramer Class III chemicals, the geometric mean of NOELs is about 3-fold higher for product ingredients as compared to the Munro chemicals.

- *Cramer Class I*: adjusted NOELs for product ingredients in Class I ranged from 5 to 11,000 mg/kg/day[5] with a geometric mean of 99 mg/kg/day. The NOELs for Cramer Class I compounds in the Munro et al. (1996) analysis ranged from 0.5 to 7203 mg/kg/day[6] with a geometric mean of 112.
- *Cramer Class II*: only two of the three product compounds in Class II had adequate toxicological data to derive a NOEL; the adjusted NOELs for these compounds were 67 and 200 mg/kg/day. Munro et al. (1996) reported adjusted NOELs ranging from 0.3 to 1441 mg/kg/day.

[4] Note that the Appendix in Munro et al. (1996) includes a column called "Calculated NOEL." These values do not include an UF of 3-fold for subchronic studies (these studies are called out with an asterisk). Therefore, the range and mean values of NOELs from this table were determined after dividing any NOEL followed by an asterisk by an UF of 3.

[5] Note—the lowest NOEL in this group was 0.5 mg/kg/day, but it was based on a free-standing NOEL, hence this value may be far below the threshold portion of the dose–response curve.

[6] NOEL for isopropyl alcohol is 0.006 (0.018 divided by an UF of 3) mg/kg/day. As described in Munro et al. (1996), there was one study which reported a NOEL for teratogenicity at a very low dose; however, its structure, known metabolism, and other toxicologic data provide no evidence for concluding teratogenicity. The next lowest NOEL for Class I was 0.5 mg/kg/day (for triethylene glycol).

Table 2
Cramer Class distribution of chemicals

Cramer Class	Munro et al. (1996) database	Chemicals used in household and personal care products
Cramer Class I	137 (22%)	92 (63%)
Cramer Class II	28 (5%)	4 (3%)
Cramer Class III	448 (73%)	49 (34%)
Total chemicals	613	145

Table 3
Comparison of NOELs (mg/kg/day) for personal and household care product chemicals and Munro et al. (1996) dataset

Cramer Class	$n=$	Lowest NOEL	Highest NOEL	Geometic mean of adjusted NOELs
Class I				
Munro database	137	0.006/0.5[a]	7203	112
Product Chemicals	21[b]	0.5/5[b]	11000	99
Class II				
Munro database	28	0.3	1441	25
Product chemicals	2	67	200	NA[c]
Class III				
Munro database	446	0.005	3775	9
Product chemicals	21	0.7	1400	30

[a] NOEL for isopropyl alcohol is 0.006 (0.018 mg/kg/day divided by 3-fold UF). As described in Munro et al. (1996), there was one study which reported a NOEL for teratogenicity at a very low dose; however, its structure, known metabolism and other toxicologic data provide no evidence for concluding teratogenicity. This value was excluded from the Summary statistics.The next lowest NOEL for Class I was 0.5 mg/kg/day (for triethylene glycol).

[b] The NOEL for butyl acetate of 0.5 was based on a free-standing NOEL with no supporting data. The next lowest value was 5 for 1,4-butanediol. The 0.5 value was excluded from the summary statistics.

[c] There are too few chemicals in this class to support the calculation of a mean value.

- *Cramer Class III*: for compounds in Class III, adjusted NOELs from the consumer product chemicals ranged from 0.7 to 1400 mg/kg/day with a geometric mean of 30 mg/kg/day. The range of adjusted NOEL values in Munro et al. (1996) was 0.005–3775 mg/kg/day and a geometric mean of 9 mg/kg/day.

4. Discussion

The intent of this analysis was 2-fold. The first goal was to confirm that the chemical categories represented in the original Munro analysis were broad enough to include the categories of compounds selected from ingredients known to be used in consumer products. The second goal was to confirm that personal and household care product chemicals from each Cramer Class (but not included in the Munro analysis), would have NOELs that would fall within the range of the NOELs identified in the original analysis. When the 248 product chemicals were assigned to chemical categories, it was found that the 92 categories to which the chemicals in the original Munro dataset were assigned covered all but 8 groups, indicating good coverage of the original dataset across the categories identified in consumer products. Oral NOEL values were located for personal and household care product chemicals from each Cramer Class to evaluate the range of NOELs for comparison with the range of NOELs reported in Munro et al. (1996). The results show that the distribution of NOELs identified from compounds used in household and personal care products falls well within the range of NOELs for the larger database analyzed by Munro et al. (1996) that was used as the basis for calculating TTC exposure limits. These data provide strong support for the relevance of the published TTC values for the three Cramer Classes for providing adequately protective benchmarks for exposure to the types of ingredients used in personal and household care products, and support the robustness of the original analysis of Munro et al. (1996).

The TTC approach has been favorably reviewed for use in the assessment of food contaminants and additives. Given that food consumption results in exposures to contaminants/additives that would be expected to occur broadly though the population and extend over a significant portion of the lifetime, it seems reasonable that similar criteria for potential exposures to personal and household care product ingredients should be sufficiently protective. The current research supports the applicability of the TTC approach to a group of chemicals used in personal and household care products and bolsters the support for use of this approach ingredients used in consumer products.

One difference between exposure via the food chain and exposure via personal and household care products is route of exposure. The primary route of exposure for many personal and household care products is dermal. In general, the skin is a significant barrier for systemic exposure to chemicals, compared to the GI tract, and as a result, NOAELs determined in dermal studies are frequently higher than those determined in oral studies. There is a long history of using oral toxicology data to support the risk assessment of materials following dermal exposures. In the absence of data on route-specific bioavailability, the assumption of equivalent oral and dermal bioavailability has been considered to be protective (European Commission, 1994a,b). Development of more refined approaches for the adjustment of oral TTC values to dermal exposures is desirable. However, in the interim, the assumption of equivalent bioavailability, in the context of the TTC approach should provide a conservative way forward.

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Appendix A

Chemical categories[a] used to group chemicals from Munro et al. (1996) and ingredients used in personal and household care products

1. Acetal (9/0)
2. Alcohols (61/27)
3. Aldehydes (13/2)
4. Alicyclic (10/4)
5. Aliphatic (17/4)
6. Alkanolamides (1/1)
7. Alkanolamines (5/4)
8. Alkene (57/6)
9. Alkoxylated Alcohols (5, 15)
10. Alkoxylated Amides (1, 0)
11. Alkoxylated Amines (0/2)
12. Alkoxylated Carboxylic Acids (0/2)
13. Alkyl Aryl Sulfonates (1/6)
14. Alkyl Ether Sulfates (2/0)
15. Alkyl Sulfates (0/1)
16. Alkylamido Alkylamines (1/1)
17. Alkyl-Substituted Amino Acids (2/4)
18. Alkyne (3/1)
19. Amides (45/11)
20. Amine Oxides (1/1)
21. Amines (57/11)
22. Amino Acids (5/6)
23. Anhydride (5/0)
24. Aromatic (220/24)
25. Aromatic Amines (104/0)
26. Azo Dye (13/7)
27. Benzophenones (0/2)
28. Betaines (0/1)
30. Biological Products (4/2)
31. Carbamate (25/1)
32. Carbohydrates (2/4)
33. Carbonate (4/0)
34. Carboxylic Acids (53/9)
35. Color Additives (4/19)
36. Cyano Guanidine (1/0)
37. Epoxide (4/0)
39. Esters (83/30)
40. Ethers (103/11)
41. Fatty Acids (0/5)
42. Fatty Alcohols (0/4)

Appendix A. (*continued*)

43. Glyceryl esters and derivatives (0/1)
44. Guanidine (3/0)
45. Halogen Compounds (173/7)
46. Heterocyclics (76/18)
47. Hydrazad (5/0)
48. Hydrazide (1/0)
49. Hydrazine (1/0)
50. Imidazoline Compounds (1/0)
51. Imides (3/0)
52. Imine (2/0)
53. Isocyanate (1/0)
54. Ketones (35/5)
55. Lactam (1/0)
56. Lactone (12/0)
57. Long chain (30/41)
58. Nitrate (1/0)
59. Nitrile (16/2)
60. Nitro (34/0)
61. Nitroamines (2/0)
62. Nitroguanadine (1/0)
63. *N*-Nitroso (1/1)
64. Organic salts (8/9)
65. Oxime (5/0)
66. Phenols (61/13)
67. Phosphorus compounds (38/3)
68. Polymeric ethers (0/4)
69. Polyols (7/7)
70. Pthalamide (4/0)
71. Quaternary ammonium (6/7)
72. Sarcosinates and sarcosines (0/2)
73. Short chain (46/28)
74. Siloxanes and silanes (1/4)
75. Soaps (1/2)
76. Sorbitan derivatives (2/4)
77. Sterols (1/0)
78. Sugars (8/0)
79. Sulfonamide (14/0)
80. Sulfone (5/0)
81. Sulfonic acid (17/17)
82. Sufonium (1/1)
83. Sulfoxide (3/0)
84. Sulfuric acid amide (4/0)
85. Sulfuric acid esters (20)
86. Terpenes (9/1)
87. Thio compounds (28/4)
88. Thio ureas (5/0)
89. Thiocarbamate (3/0)
90. Thiophosphate)4/0)
91. Unsaponifiables (1/0)
92. Urea (17/0)

[a] Categories are not exclusive, chemicals may appear in multiple categories. Values in parentheses show counts of the number of chemicals in the Munro et al./product datasets.

Appendix B

NOELs for selected chemicals ordered by Cramer structural class

Chemical name	CASRN	Species	Exposure duration	Administered doses (mg/kg-day)	Study LOEL (mg/kg-day)	Study NOEL (mg/kg-day)	Adjusted NOEL (mg/kg-day)	Reference
Structural Class I								
Acid blue 1	129-17-9	Mouse	2 years	0, 150, 450, 1500	1500	450	450	IFREB (1981)
Butanediol, 1,4-	110-63-4	Rat	28 days	0, 5, 50, 500	500	50	5	Jedrychowski et al. (1990)
Butyl acetate	123-86-4	Rat	6 months	0, 0.5	None	>0.5	0.5	Petrovskaya and Bul'bin (1969)
Butyl carbitol	112-34-5	Rat	13 weeks	0, 50, 250, 1000	1000	250	83	Johnson et al. (2005)
C.I. Fluorescent Brightener 220	16470-24-9	Rabbit	GD 7-28	0, 100, 400, 800	400	100	100	Turck (2000)
C.I. Fluorescent Brightener 244	16090-02-1	Rat	2 years	0, 12, 64, 656[a]	656	64	64	Bomhard and Löser, 1978
Citric acid	77-92-9	Rat	2 years	0, 1500, 2300	1500	None	500	Horn et al. (1957)
D&C Orange No. 4	633-96-5	Rat	13 weeks	0, 130, 690, 3700	130	None	43	Singh et al. (1987)
Decyl oleate	3687-46-5	Rat	28 days	0, 100, 500, 1000 (5-day/week)	None	>700	70	Potokar et al. (1987)
Dodecanol	112-53-8	Rat	37 days	0, 100, 500, 2000	500	100	10	Hansen (1992)
Ethanolamine	141-43-5	Rat	13 weeks	0, 160, 320, 640, 1280, and 2670	640	320	107	Mellon Institute (1950); Smyth et al. (1951)
FD&C Yellow No. 5	1934-21-0	Rat	2 years	0, 53, 540, 1105, 3000[b]	None	>3000	3000	Borzelleca and Hallagan (1988)
Hexadecanol	36653-82-4	Rat	13 weeks	0, 577, 1440, 3500	1440	577	192	Vista Chemical (1992)
Hexylene glycol	107-41-5	Rat	28 days	0, 50, 100, 1000	1000	100	10	Smith (1995)
Methyl salicylate	119-36-8	Rat	2 years	0, 74, 370, 735, 1470[b]	370	74	74	Webb and Hansen (1963)
Niacinamide	98-92-0	Rat	12 weeks	0, 100, 200, 400	200	100	33	Horger and Gerheim (1958)
Octadecanol	112-92-5	Rat	28 days	0, 100, 500, 1000 (5-day/week)	None	>700	70	Potokar and Henkel (1986)
Salicylic acid	69-72-7	Rat	GD 8-14	0, 62, 102, 205, 410	62	None	21	Tanaka et al. (1973)
Sodium cumene sulfonate	28348-53-0	Rat	13 weeks	0, 400, 800, 1200	800	400	133	Greim et al. (1994)
Sodium lauryl sulfate	151-21-3	Rat	2 years	0, 180, 350, 700	None	>700	700	Fitzhugh and Nelson (1948)
Sorbitol	50-70-4	Rat	17 months	0, 7400, 11000	None	>11000	11000	LeBreton (1956)
Triethyl citrate	77-93-0	Rat	42 days	0, 1000, 2000, 4000	None	>4000	400	Finkelstein and Gold (1959)
Structural Class II								
Gluconolactone	90-80-2	Rat	29 months	200 mg/kg[b]	None	200	200	Van Logten et al. (1972)

Panthenol	81-13-0	Rat	13 weeks	0, 20, 50, 200	None	200	67	NAS/NRC (1974); European Commission (2002); Expert Group on Vitamins and Minerals (2002)
Structural Class III								
Acid yellow 17	6359-98-4	Rat	13 weeks	0, 8.5, 82, 820[b]	820	82	27	Gaunt et al. (1971)
Ascorbyl Palmitate	137-66-6	Rat	9 months	0,1400, 3500	3500	1400	1400	Fitzhugh and Nelson (1946)
Benzophenone	119-61-9	Rabbit	GD 6-29	0, 5, 25, 45	25	5	5	NTP (2004a)
Benzophenone-3	131-57-7	Rat	13 weeks	0, 200, 410, 830, 1700, 3500[b]	830	410	137	NTP (1992a)
Benzotriazole	95-14-7	Rat	2 years	0, 560, 1000	560	None	190	NCI (1978)
Cetrimonium bromide	57-09-0	Rat	1 year	0, 10, 20, 45	45	20	20	Kabara (1984)
Diazolidinyl urea	78491-02-8	Rat	13 weeks	0, 1, 2, 9	None	>9	3	Leberco Laboratories (1981)
Diethanolamine	111-42-2	Rat	13 weeks	0, 14, 32, 57, 124, 242	32	14	5	NTP (1992b)
Dimethylpro pylenediamine, *N*,*N*-	109-55-7	Rat	28 days	0, 10, 50, 250	250	50	5	Hoechst (1996)
Dipropylene glycol	25265-71-8	Rat	2 years	0, 115, 470, 3040	470	115	115	NTP (2004b)
Distearyldimonium chloride	107-64-2	Rat	28 days	0, 20, 100, 500	500	100	10	Hoechst (1990)
DMDM Hydantoin	6440-58-0	Rat	13 weeks	0, 100, 200, 400	None	>400	130	FDRL (1982)
Iodopropynyl butylcarbamate	55406-53-6	Rat	2 years	0, 20, 40, 80	40	20	20	Inversk Research International (1989)
Maleic acid	110-16-7	Rat	13 weeks	0, 10, 55, 550	None	>550	180	Hazleton (1977)
Methylisothiazolinone/ Methylchloroiso-thiazolinone mixture	2682-20-4/ 26172-55-4	Rat	13 weeks	0, 3, 8, 20	20	8	3	Rohm and Haas Co. (1984)
Octocrylene	6197-30-4	Rat	13 weeks	0, 58, 175, 340, 1085	340	175	58	BASF (1993)
Sodium lauroyl sarcosinate	137-16-6	Rat	2 years	0, 155, 780, 1400	780	155	155	Technology Sciences Group Inc. (1994)
Tetraethylene glycol	112-60-7	Rat	2–6 months	6.8 to 680	6.8	None	0.7	Schladt et al. (1998)
Triclosan	3380-34-5	Rat	1–2 years	0, 22, 73, 220, 440	220	73	73	Pathco Inc (1990)
Triethanolamine[2]	102-71-6	Rat	13 weeks	0, 5, 80, 170, 730, 1270, 2610	170	80	27	Smyth et al. (1951)
Trisodium ethylenediamine disuccinate	20846-91-7	Rat	13 weeks	0, 50, 300, 700, 1000	700	300	100	Dotti et al. (1995)

GD, gestation day.

[a] The reported dose is the arithmetic average of the male and female dose for that dietary group.

[b] Normally a single dose study would not be acceptable, however, this study was evaluated in the context of the other supporting data reviewed by WHO that support that this dose as a free-standing NOEL provides a very conservative estimate of the NOEL for this compound.

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